IN THE MATTER OF

Austrian Patent Application A 1828/1998

of Dr. Andreas BERNKOP-SCHNÜRCH

I, Felicia Marchardt, Riemergasse 14, A 1010 Vienna, Austria declare that I am conversant with the German and English language and that I am the translator of the priority document attached, and I certify that to the best of my knowledge and belief the attached document is a true and correct translation of the original text of the above Austrian patent application.

Felicia Marchardt

Signed this 4th day of August 2006

Central Services

Administrative Head Office

(logo): austrian patent office

Dresdner Straße 87
1200 Vienna
Austria

www.patentamt.at

Office Fee € 6.00
Document Fee € 39.00

Filing number A 1828/1998

It is herewith certified by the Austrian Patent Office that

Mag. Dr. Andreas Bernkop-Schnürch
in A-1050 Vienna, Christophgasse 6/11

on 4 November 1998 filed a patent application relating to

"Method of Improving the Adhesion of Bioadhesive Polymers"

and that the specification herewith annexed is identical with the specification as originally filed together with this patent application.

It has been requested to name Mag.pharm. Dr. Andreas Bernkop-Schnürch in Vienna as inventor.

Austrian Patent Office
Vienna, 22 June 2006
The President:

HRNCIR
Fachoberinspektor

(Seal: AUSTRIAN PATENT OFFICE)
(Stamp: austrian patent office)

A1828/98-1 51. Int. Cl.

Original

AUSTRIAN PATENT SPECIFICATION 11 No.

---

73 Proprietor of Patent: ANDREAS BERNKOP-SCHNÜRCH Mag.pharm.Dr. Vienna (AT)

54 Subject: METHOD OF IMPROVING THE ADHESION OF BIOADHESIVE POLYMERS

61 Addition to Patent No.

67 Conversion from Utility Model

62 Division from:

22 21 Filed on:

33 32 31 Convention Priority:

42 Beginning of Patent Duration:

Longest Possible Duration:

45 Issued on:

72 Inventor(s): ANDREAS BERNKOP-SCHNÜRCH Mag.pharm.Dr. CHRISTOPHG.6/11, 1050 VIENNA (AT)

60 Dependence:

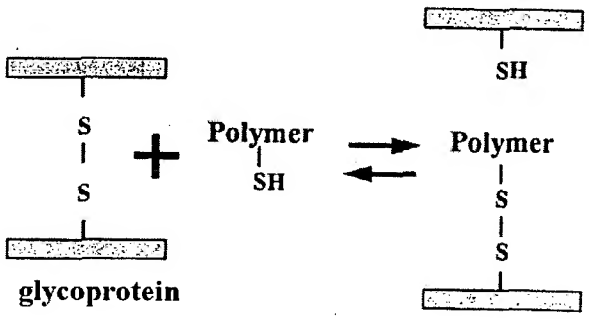
---

56 Printed publications that have been taken into consideration for judging the patentability:

SPECIFICATION:

The invention described in the following relates to the field of pharmaceutical technology.
By this invention, the adhesion of bioadhesive polymers, particularly to mucous membranes of the gastro-intestinal tract, of the eye, of the nasopharyngeal space as well as of the lung, vagina and buccal cavity is to be markedly improved.
To date, an adhesion of bioadhesive polymers could only be obtained by forming non-covalent bonds, such as, e.g., hydrogen bridge bonds and ionic interactions between mucosa and polymer. However, the introduction of partial thiol structures into bioadhesive polymers enables the additional formation of covalent bonds in the form of disulfide bridge bonds between the polymer and disulfide, or partial thiol structures, respectively, of the mucous layer (cf. Fig. 1).
Since these modified polymers are polymers comprising partial thiol structures, they are termed "**thiomers**".

Fig. 1 Schematic representation of the binding of a polymer with thiol-groups to a glycoprotein of the mucous layer.



The synthesis of thiomers can also be effected by reaction of polymers with partial carboxylic acid structures, such as, e.g., poly(acrylic acid) derivatives with cysteine under formation of amide bonds between this amino acid and the polymer. The reaction is mediated by coupling reagents, such as, e.g., 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide-hydrochloride. The partial

structures forming therein are illustrated in Fig. 2.

Practical implementation:

10 g of polycarbophil, corresponding to a monograph of the United States Pharmacopoeia (USP), are suspended in portions in 100 ml of a 4% (m/m) methanolic NaOH solution under continuous stirring. The sodium salt of the polymer thus forming is filtered off and washed with methanol until the filtrate has a neutral pH. Subsequently, the polymer is dried at room temperature in the exsiccator. One gram of neutralised polycarbophil is hydrated in 250 ml of demineralised water, and the carboxylic acid groups of the polymer are pre-activated for 45 minutes at room temperature by 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide-hydrochloride, which is added at a final concentration of 50 mM under stirring. In order to prevent an oxidation of the L-cysteine subsequently added, the pH of the solution is adjusted with 5 N HCl to pH 4 and it is exposed to N_2-gas for 15 minutes. After the addition of 0.5 g of L-cysteine, the pH of the solution optionally is re-adjusted to pH 4-5 with HCl, or NaOH, respectively, and the reaction mixture is stirred for 3 hours at room temperature under exposure to N_2-gas. The polycarbophil-cysteine-conjugate is dialysed against an aqueous 1 mM HCl and 2 µM EDTA solution, twice against the same dialysis medium, yet additionally containing 1% NaCl, and finally, exhaustively against 0.5 mM HCl at 10°C under the exclusion of light. The isolated conjugate is neutralized with 2 N NaOH and lyophilized at -30°C. Storage is effected at 4°C.

The polymer-cysteine conjugate described here exhibits a markedly higher adhesion capacity in the adhesion test on an excised mucosa from porcine small intestine in artificial intestinal fluid, consisting of 50 mM Tris-HCl buffer, pH 6.8, containing 0.9% NaCl, than does polycarbophil pre-treated in the same manner, to which, however, no cysteine had been covalently bound.

Properties of polymers with partial thiol structures

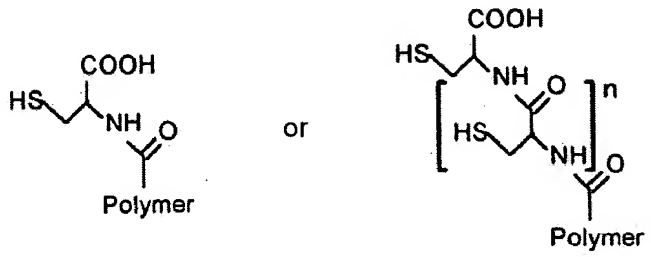
(I) Compared to corresponding polymers which do not comprise thiol groups, the polymers described here are characterised by a markedly enhanced adhesion to the mucosa.

(II) By the formation of disulphide bridges within the polymer

swelling in aqueous solutions, the viscosity and cohesion markedly increase.

(III) Polymers having thiol groups have reducing properties.

Fig. 2 Schematic illustration



CLAIMS:

1. A method of producing polymers comprising partial thiol structures in their entire structure, characterised in that polymers which have partial carboxylic acid structures are reacted with thiols which comprise primary amino groups by using coupling agents, such as, e.g., carbodiimides.

2. A method of producing polymers comprising partial thiol structures in their entire structure, characterised in that polymers which have primary amino groups are reacted with thiols which comprise partial carboxylic acid structures, by using coupling agents, such as, e.g., carbodiimides.

3. The term Thiomer(e) as well as English thiomer(s) for polymers comprising partial thiol structures.

4. The term Tiomer(e) as well as English tiomer(s) for polymers comprising partial thiol structures.

5. Polymers whose adhesion to mucous membranes is improved by the introduction of thiol groups into their chemical structure.

6. Forms of administration for medicaments and cosmetics whose adhesion to mucous membranes is improved by the introduction of thiol groups.

7. Medicaments and cosmetics comprising polymers with partial thiol structures.

8. Implants comprising polymers with partial thiol structures.

9. Contact lenses comprising polymers with partial thiol structures.

10. Polymers with partial thiol structures as carrier matrix for medicaments.

11. Polymers with partial thiol structures as carrier matrix for vaccines.

12. The use of polymers with partial thiol structures as a coating material for administration forms, such as, e.g., tablets, pellets, microparticles and nanoparticles.

13. Polymers whose adhesion to mucous membranes is improved by the formation of covalent bonds of any type.

14. Polymers having partial thiol structures, which are used for inhibiting proteases.

15. the use of polymers having partial thiol structures as a carrier matrix for controlled active substance release systems.

ABSTRACT:

The invention described here relates to bioadhesive polymers, whose adhesion can be markedly improved by the introduction of thiol groups into their respective chemical structure. This improved adhesion is based on the formation of disulfide bridge bonds between the modified polymer - thiomer in short - and disulphide- or partial thiol structures of the mucous layer.